Exp Brain Res (2007) 181:131–137
DOI 10.1007/s00221-007-0912-5

RESEARCH ARTICLE

Dopaminergic influences on changes in human tactile acuity induced by tactile coactivation

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Received: 14 November 2006 / Accepted: 13 February 2007 / Published online: 8 March 2007

Abstract As shown in animal experiments, dopaminergic mechanisms participate in *N*-methyl-D-aspartate (NMDA) receptor-dependent neuroplasticity. Dopamine is thought to play a similar role in humans, where it influences learning and memory. Here, we tested the dopaminergic action on learning in the tactile domain. To induce tactile non-associative learning, we applied a tactile coactivation protocol, which is known to improve tactile two-point discrimination of the stimulated finger. We studied the influence of a single oral dose of levodopa (25, 50, 100, 250 or 350 mg) administered preceding the coactivation protocol on changes in tactile performance in different groups of subjects. In addition, 3 × 100 mg levodopa was administered over a time period of 3 h in another group. Under placebo conditions, tactile two-point discrimination was improved on the coactivated index finger. Similar improvement was found when 25, 50 and 250 mg levodopa was applied. On the contrary, tactile improvement was completely eliminated by 1 × 100 and 3 × 100 mg levodopa. No drug effects were found on the left index finger indicating that the drug had no effect on performance per se. In contrast to previous findings in the motor and speech domain, we found that the administration of levodopa exerts either no or even negative effects on non-associative learning in the human somatosensory system. Whenever levodopa is used in neurorehabilitative context, it has to be kept in mind that beneficial effects in the motor or speech domain cannot be easily generalized to other systems.

Keywords Perceptual learning · Plasticity · Pharmacological modulation · Somatosensory

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Introduction

Extensive practice and training improves perceptual or motor performance and is associated with specific changes of cortical representations (Recanzone et al. 1992; Fahle and Poggio 2002). On a cellular level, learning appears to be based on various mechanisms including changes in synaptic efficacy, most often referred to as long-term potentiation (LTP) or long-term depression (LTD). In animal experiments, dopaminergic mechanisms stabilize these processes (Otani et al. 1998; Bailey et al. 2000). It was demonstrated that D1 receptor activity has an enhancing effect on the induction and consolidation of LTP (Bach et al. 1999; Bailey et al. 2000; Gurden et al. 2000; Huang et al. 2004) as well as a facilitating effect on LTD induction (Chen et al. 1996; Huang et al. 2004). The impact of D2 receptors on LTP and LTD has been described ambiguously. With regard to LTP, D2 receptor activation has been shown to be positive (Manahan-Vaughan and Kulla 2003), negative (Frey et al. 1989) or without effect (Gurden et al. 2000).

LTD has been observed to be enhanced by D2 receptor activity (Otani et al. 1998; Spencer and Murphy 2000), but can also be inhibited (Chen et al. 1996).

While there is substantial knowledge about dopaminergic action on cellular aspects of learning, dopaminergic modulation of plastic changes in humans remains to be clarified. Evidence exists for the participation of catecholamines in human plasticity. As previously shown, amphetamine stabilizes use-dependent motor cortex plasticity (Butefisch et al. 2002; Sawaki et al. 2002), accelerates recovery of motor function in stroke patients (Walker-Batson et al. 1995) and improves learning and consolidation of verbal material (Soetens et al. 1993, 1995). A possible explanation for the action of amphetamines could be the stabilization of NMDA receptor-induced plasticity through increased availability of catecholamines. Recent work has demonstrated that application of a single dose of levodopa significantly improves the formation of a motor memory in healthy subjects as well as in chronic stroke patients (Floel et al. 2005a, b). Similarly, word learning in healthy subjects is enhanced by levodopa (Knecht et al. 2004).

To study dopaminergic influences in the tactile domain, we applied a tactile coactivation protocol. This protocol is based on task-unrelated, passive and unattended stimulation of the finger tip inducing an improvement in tactile acuity that is paralleled by an enlargement and shift of cortical representations of stimulated skin sites. Coactivation does not imply factors such as attention or reward and can, thus, be considered as form of non-associative learning (Godde et al. 1996, 2000; Pleger et al. 2001, 2003).

Evidence has been provided that NMDA-receptor activation is required for the manifestation of this specific type of fast, stimulation-induced improvement in tactile acuity as memantine, a substance known to block selectively NMDA receptors completely eliminates both changes in discrimination thresholds and cortical reorganization. On the other hand, amphetamine results in almost a doubling of the normally observed improvement of tactile acuity and cortical reorganization (Dinse et al. 2003). The positive action of amphetamine suggested the participation of dopaminergic or noradrenergic modulation in mediating coactivation-induced effects.

The aim of the present study is to determine whether enhanced availability of dopamine influences coactivation induced changes in the tactile domain. We assessed the effectiveness of levodopa premedication to modulate the typically observed stimulation-induced improvement of tactile discrimination performance by testing a broad range of levodopa concentrations. We hypothesised that in a dose-dependent manner subjects would show enhanced performance improvement compared to placebo conditions.

Materials and methods

Experimental groups

We tested 54 right-handed subjects of both sexes (19–33 years of age, 22 males, 32 females): 12 subjects provided a placebo-controlled baseline, the remaining subjects were subdivided in different groups to test the effects of levodopa concentrations. Eight subjects were tested under 1×100 and 3×100 mg, 7 subjects under 25, 50 and 250 mg and 5 subjects under 350 mg of levodopa, respectively. Subjects allocated to different experimental groups were matched according to their age and gender. The study was performed in accordance with the Declaration of Helsinki. The subjects gave their written consent, and the protocol was approved by the local ethical committee of Ruhr-University Bochum. General exclusion criteria were a history of neurological and psychiatric disorders, chronic or acute disease and the intake of drugs affecting the central nervous system.

Experimental design

First, discrimination thresholds of the index finger were measured using the method of constant stimuli in a simultaneous spatial two-point discrimination task as described previously to assess tactile acuity (Godde et al. 1996, 2000; Pleger et al. 2001, 2003; Ragert et al. 2004). In this task, seven pairs of needles with distances between 0.7 and 2.5 mm were used. For controls and to assess false alarm rates, zero distance was tested by using a single needle. Subjects were instructed that there were single needles for control, but not how often they were presented. The needles were placed on a rotable disc allowing to switch rapidly between distances. The disc was installed on a plate that could be moved up and down. The test finger came in contact with the needles whenever the plate was moved down. The subject had to decide immediately after touching the needles whether he or she had the sensation of one or two tips. No feedback was given. Each distance was tested 8 times in a randomized order, resulting in 64 trials per session. To obtain stable discrimination thresholds, four sessions were done before intervention. The summed responses were plotted against distance as a psychometric function for absolute threshold and fitted by a binary logistic regression. The distance yielding 50% correct responses was considered the threshold for the individual subject (Fig. 1).

Secondly, we applied a tactile coactivation protocol. The protocol was the same as in our previous studies aiming at coactivating a large number of receptive fields on the tip of the index finger in a Hebbian manner to strengthen their mutual interconnectedness (Hebb 1949; Godde et al. 1996,

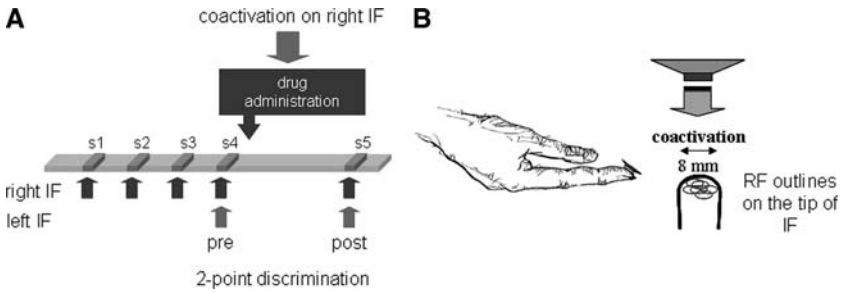

Fig. 1 **a** Experimental design. Session 1–4 (*s1–s4*) served to create a stable discrimination performance for the right index finger (IF). The left IF was tested as control at *s4* (pre-stimulation) and after stimulation (session *s5*, post). A single dose of levodopa was applied at the beginning of tactile coactivation. Alternatively, 100 mg of levodopa was administered three times at the beginning of stimulation, after 1 and after 2 h to keep plasma levels high throughout the period of stimulation. **b** Application of tactile coactivation. A small solenoid with a diameter of 8 mm was mounted on the tip of the right IF to coactivate the receptive fields (RFs) representing the skin portion under the solenoid (50 mm^2)

2000; Pleger et al. 2001, 2003; Dinse et al. 2003; Ragert et al. 2004). Tactile coactivation was applied to the tip of the right index-finger. Tactile stimuli used for coactivation were drawn from a Poisson process at interstimulus-intervals between 100 and 3,000 ms with a mean frequency of 1 Hz. To apply stimulation, a small device consisting of a small solenoid with a diameter of 8 mm was used, which was taped to the right index finger. Pulses were recorded in MP3 format and played back via a portable player permitting the subjects' unrestrained mobility. Coactivation stimuli were applied at suprathreshold intensities. Laser vibrometer measurements showed that the actual amplitude of skin displacement was 80–100 μm. During the stimulation time of 3 h, all subjects resumed their daily routines.

After coactivation, another session of two-point discrimination was performed. In addition, the index finger of the contralateral hand was tested before and after intervention in order to exclude unspecific side-effects of the drugs to the contralateral non-coactivated hand.

A single oral dose of levodopa (25, 50, 100, 250 or 350 mg) in combination with benserazid, a dopa-decarboxylase inhibitor, was administered at the onset of peripheral tactile stimulation. The placebo group received a standard placebo substance in identical capsules. Plasma levels were assayed from blood samples taken in each subjects after 30, 60 and 90 min. To keep drug plasma levels high during the entire period of stimulation, 100 mg of levodopa was administered at the beginning of tactile coactivation, and after 60 and 120 min in one experimental group. In these subjects, blood samples were taken after 60 and 120 min.

Blood specimens for estimation of levodopa were placed in EDTA-test tubes containing 100:1 of 0.5% sodium disulfite solution. Within 10 min the samples were centrifuged for 15 min, at 300*g* and 10°C. The resulting supernatant (plasma) was decanted and stored at −80°C. We used reversed-phase HPLC (high performance liquid chromatography) with electrochemical detection for estimation of levodopa in plasma (Gerlach et al. 1986).

In statistical analysis our primary outcome measures was defined as the performance improvement after coactivation. To test that this improvement depends on the levodopa concentration, we performed a repeated measures ANOVA with the factors SESSION (pre vs. post) × DOSAGE (Placebo, 25, 50, 100, 3 × 100 and 250 mg). A paired *t*-test was employed to confine significant differences between the pre and the post session for each dosage separately.

Additionally, relative changes in the two-point discrimination task were compared in a univariate ANOVA with the factor DOSAGE.

Results

This study was performed in a double-blind design. Neither the experimentator nor the subjects were aware of the medication status. However, during the experiment subjects were asked several times whether they experienced any of the expected side-effects (e.g., nausea, fatigue). We observed no difference between the placebo group and the experimental groups, except for the subjects having ingested 350 mg levodopa. In this group two subjects complained of severe nausea during or after the experiment. Therefore we decided not to proceed with the application of 350 mg and the experimental group was excluded from further analysis.

During the initial four sessions of pre-stimulation, all subjects met the criterion of stable baseline performance (ANOVA sessions s1–s4-pre $F(3,144) = 1.123$, $P = 0.342$).

The repeated measures ANOVA with the factors SESSION (pre, post) and DOSAGE (Placebo, 25, 50, 100, 3 × 100 and 250 mg) yielded a significant interaction ($F(5,240) = 2.696$, $P = 0.03$). In placebo-controlled subjects, 3 h of tactile coactivation on the tip of the right IF lowered discrimination thresholds for the spatial two-point discrimination task ($P = 0.001$) thereby confirming previous findings (Godde et al. 1996, 2000; Pleger et al. 2001,

Table 1 Absolute discrimination thresholds in mm of the right (s1–s3, pre and post) and the left index finger (left pre and left post)

Concentration	Number of subjects	s1	s2	s3	Pre	Post	Left pre	Left post
Placebo	12	1.53	1.54	1.51	1.49	1.27	1.47	1.4
3 × 100 mg	8	1.69	1.56	1.6	1.58	1.52	1.6	1.6
1 × 100 mg	8	1.56	1.61	1.64	1.57	1.62	1.72	1.61
250 mg	7	1.55	1.44	1.5	1.48	1.28	1.44	1.49
50 mg	7	1.64	1.61	1.6	1.57	1.38	1.46	1.51
25 mg	7	1.66	1.65	1.66	1.65	1.42	1.48	1.55

2003; Dinse et al. 2003). After intervention, psychometric functions showed a significant shift of thresholds toward smaller separation distances. As a control, and to demonstrate the specificity of the stimulation-induced changes, we measured thresholds of the IF of the left hand, which had not been stimulated. Thresholds remained unchanged ($P = 0.376$). For absolute discrimination thresholds in mm see Table 1 (Fig. 2).

A similar gain in discrimination abilities was found in the dosage groups of 25 mg ($P = 0.036$), 50 mg ($P = 0.002$) and 250 mg ($P = 0.01$). When comparing the percentage change in discrimination thresholds, no difference was found between placebo-controlled subjects and subjects having taken 25, 50 and 250 mg of levodopa (25 mg $P = 0.885$, 50 mg $P = 0.748$, 250 mg $P = 0.901$) (Fig. 3).

In contrast, application of 1 × 100 and 3 × 100 mg levodopa completely eliminated improvement in tactile acuity induced by coactivation. No changes in discrimination thresholds were observed (1×100 mg $P = 0.375$; 3 × 100 mg $P = 0.376$). Percentage changes in discrimination abilities were significantly different from placebo condition ($F(5,240) = 3.341$, $P = 0.012$, LSD Post Hoc comparison Placebo-1 × 100 mg $P = 0.006$, Placebo-3 × 100 mg $P = 0.01$). Given that levodopa might exert non-specific side effects, it was important to show that the drug did not affect spatial discrimination per se. This was confirmed by demonstrating that there were no effects on the left non-stimulated index finger ($F(1,36) = 0.06$, $P = 0.808$).

Plasma levels assayed from blood samples reached their maximal level after 30 min when a single dose of 50 mg levodopa was applied (223 ng/ml, SE 68 ng/ml) and after 60 min when a single dose of 25 mg (48 ng/ml, SE 10 ng/ml), 100 mg (482 ng/ml, SE 56 ng/ml) or 250 mg (720 ng/ml, SE 71 ng/ml) was administered. In the experimental group having taken 3 × 100 mg levodopa, plasma levels still remained high after 120 min (548 ng/ml, SE 29 ng/ml). Due to technical problems, i.e., some samples were corrupted due to inadequate cooling, the mean plasma levels of the group receiving 3 × 100 mg levodopa at 60 min were assessed only in 3 subjects. Therefore no values were given. As described for 120 min, the plasma level remained high in this group. We found a significant difference in plasma levels between the dosage groups 60 min (ANOVA $F(3,20) = 24.887$, $P < 0.001$) and 90 min after drug application (ANOVA $F(3,19) = 13.995$, $P < 0.001$).

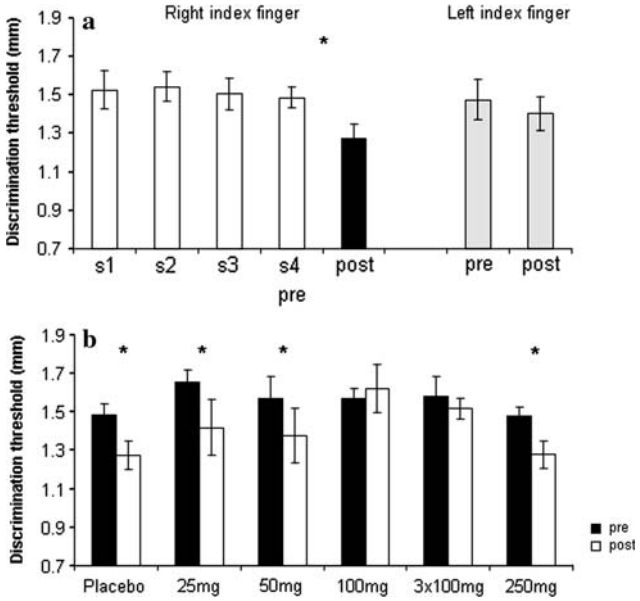

Fig. 2 Psychophysical effects of tactile coactivation. **a** Placebo group ($n = 12$). Discrimination thresholds were stable before intervention (*s1–s4*). After coactivation, discrimination thresholds on the right IF are significantly reduced, whereas thresholds of the left IF remain unaffected. **b** Discrimination thresholds of the right IF before (*pre*) and after (*post*) stimulation in different dosage groups. A significant reduction of discrimination thresholds was observed in the placebo group and when *25* mg ($n = 7$), *50* mg ($n = 7$) or *250* mg ($n = 7$) levodopa was applied. On the contrary, thresholds did not change in the *1 × 100* and *3 × 100* mg group. *Bars* represent standard error

Discussion

Our results indicate that the degree of improvements in tactile acuity evoked by a coactivation protocol can be gated by dopaminergic mechanisms in a dose-dependent manner. However, the details of that gating are not in line with recent findings reported for motor and speech domains. The administration of 25, 50 and 250 mg levodopa during coactivation induced an improvement in tactile acuity similar to that observed under placebo conditions indicating that these

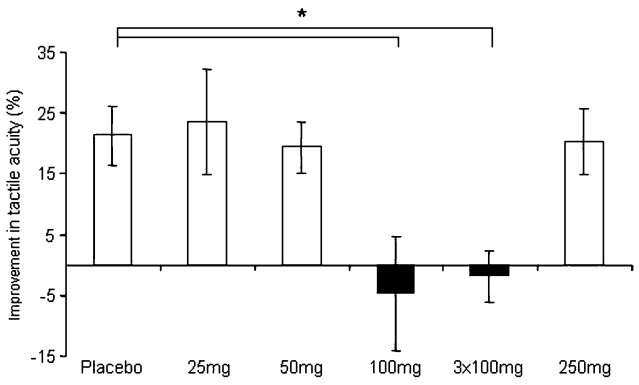

Fig. 3 Percentage changes in discrimination thresholds across all experimental groups. No significant difference between placebo controlled subjects and subjects that had been applied *25*, *50* and *250* mg levodopa was found. In contrast to placebo conditions, *100* and *3* × *100* mg levodopa completely blocked improvement in tactile acuity

concentrations had no enhancing effect. In contrast, 1 × 100 and 3 × 100 mg levodopa applied during the intervention completely eliminated stimulation induced improvements in tactile acuity. Accordingly, levodopa over a wide concentration range evoked no effects, but blocked non-associative learning of tactile discrimination performance within a small range of concentrations.

Generally, substances such as those used in our study might evoke severe side effects due to global excitability changes, disturbance of the excitation–inhibition balance, or attentional differences. As shown many times before, improvement in discrimination performance is highly specific to the stimulated fingers; there is no transfer to fingers of the other hand (Pleger et al. 2001, 2003; Dinse et al. 2003). We therefore used the performance of the left index finger to measure the specificity of the observed drug effects. For none of the concentrations tested, levodopa had an effect on spatial discrimination performance per se. This fact, together with the consistency of the effects across subjects, supports the specific nature of the drug influence observed for the right index finger.

On a cellular level, dopamine acts on at least five receptor subtypes, D1, D2, D3, D4 and D5. Based on their ability to either stimulate or inhibit cyclic adenylate cyclase (cAMP), dopamine receptors were classified into two categories: D1-like, including D1 and D5, and D2-like, including D2, D3 and D4 (Civelli et al. 1993). There is agreement that dopamine increases NMDA currents through D1 receptors (Seamans and Yang 2004). Both D1 and NMDA receptors were suggested to contribute to the mechanisms of LTP by inducing the accumulation of cAMP and activation PKA. On the contrary, a cooperative action of D2 and NMDA receptors in LTP induction would decrease the amount of cAMP, and attenuate the involvement of PKA for LTP, or would even favor the induction of LTD instead of LTP. In most animal experiments D1 receptors enhanced neuroplasticity, whereas the impact of D2 receptors on neuroplasticity was ambiguous (Jay 2003). With regard to LTP, D2 receptor activation has been shown to be positive (Manahan-Vaughan and Kulla 2003), negative (Frey et al. 1989) or without effect (Gurden et al. 2000). LTD was enhanced by D2 receptor activity (Otani et al. 1998; Spencer and Murphy 2000), but was also inhibited in other experiments (Chen et al. 1996).

Furthermore a clear dose-dependency of the dopamine modulation of NMDA currents was found. By applying low doses of dopamine or D1 agonists in vitro, NMDA currents were potentiated whereas high dose application lead to an attenuation (Seamans and Yang 2004). Similarly, on a behavioral level, the functional role of dopamine in short-term memory processes appears to depend on cortical dopamine levels. For example, Goldman-Rakic et al. suggested that D1 receptor activation follows an inverted 'U'-shape function in case of delay-period activity on a working memory task, where too less and too much D1 agonist stimulation both disrupt performance (Goldman-Rakic et al. 2000).

In conclusion, differences in dopamine content and dopamine receptor subtype distribution, and as a result, difference in the level of dopamine receptor activation during LTP or LTD induction could explain regional discrepancies observed on the action of dopamine on synaptic plasticity (Jay 2003).

Our findings suggest that levodopa impairs stimulation induced changes in tactile acuity in a dose-dependent manner. During application of both low- and high-dose of levodopa, subjects showed improvements in tactile acuity similar to placebo condition whereas intermediate levodopa dosage completely blocked improvement in discrimination performance. Importantly, in line with the different levodopa concentrations administered, dopamine plasma concentrations also differed significantly. Given that dopamine levels in the brain are proportional to blood plasma concentrations, we can assume that the observed differences in improvement between dosage groups are in fact due to differential dopamine brain levels. These results suggest a 'U'-shape dose response characteristics as proposed previously (Goldman-Rakic et al. 2000). However, as one experimental group in the high concentration range, namely 350 mg levodopa, was excluded from further analysis, our data do not sufficiently confirm this notion.

Interestingly, in the motor domain the same dose of levodopa as used in our study was demonstrated to exert beneficial effects on memory formation. As shown by Floel et al. levodopa significantly shortened the training time required to form a motor memory in young healthy volunteers and restored the ability to form a motor memory in elderly to levels similar to those seen on healthy young

subjects. The motor training paradigm used in this study consisted of voluntary thumb movements performed at 1 Hz (Floel et al. 2005a). A recent study by Meintzschel et al. provides further evidence for a beneficial effect of dopaminergic enhancement on motor memory formation. Here the dopamine receptor agonist cabergoline enhanced motor learning, whereas it was blocked by the dopamine antagonist haloperidol (Meintzschel and Ziemann 2006). The beneficial effect of cabergoline on motor learning is associated with a shift in the balance of excitation and inhibition towards more inhibition (Korchounov et al. 2006).

Applying transcranial direct current stimulation over human motor cortex, a critical role of D2 receptor activation was suggested for the consolidation-enhancing effect following assessment of cortical excitability (Nitsche et al. 2006).

Levodopa, administered daily for 5 days in the same dose as used in the current study, was also demonstrated to enhance the speed, overall success, and long-term retention of novel word learning presumably by enhancing the stimulus salience (Knecht et al. 2004). Interestingly, application of amphetamine resulted in an even stronger enhancing effect (Breitenstein et al. 2006a), which was discussed in respect to a noradrenergic rather than dopaminergic action. This notion was supported by Breitenstein et al. who demonstrated that pergolide, a D2 receptor agonist, even impaired associative learning in healthy subjects (Breitenstein et al. 2006b).

Discrepancies between our findings in the tactile domain and those described previously in the motor domain might be explained by differences in the learning paradigms used. Tactile coactivation is a task-unrelated, passive and therefore unattended stimulation protocol. In fact, there is agreement that plastic changes can be evoked by the variation of input statistics alone, without invoking attention or reinforcement. Even more important, plastic changes can be induced without intense training as perceptual learning occurs without awareness of the stimuli solely through the repetitive exposure to stimuli (Watanabe et al. 2001). A fundamental difference between perceptual and motor memories is that the latter usually requires the actual performance of voluntary movements, which can not be accurately executed without attentional awareness (Lotze et al. 2003).

Accordingly, motor learning is assumed to involve active repetitive movement execution which induces a type of reorganization of neuronal networks that in turn mediates motions and encoding of kinematic details of the practiced movement. Similarly, word learning is based on active processes demanding massive training involving high levels of attention and working memory. The efficacy of levodopa in enhancing both motor and word learning might thus depend on the fact that in both cases task-specific memory contents are acquired actively, which suggest the involvement of systems mediating attention and working memory.

Another or additional explanation of our findings is based on possible modality- and area-specificities of dopaminergic receptor distributions. For example, differential dopamine receptor subtype distribution in somatosensory and motor regions and, as a consequence, differences in the levels of dopamine receptor activation when levodopa is applied might lead to either enhancement or blockage of learning processes—depending on the cortical and subcortical systems involved in the learning process. In particular, the close interconnectedness of the motor system with the basal ganglia might provide specific pharmacological substrates required for the motor-specific type of levodopa action observed. Tyrosin Hydroxylase(TH)-labeled fibers, i.e., dopaminergic projections, are in general distributed throughout the entire neocortex, but have striking pattern of regional specialization. For example, primary motor cortex contains the greatest density of TH-labeled fibers, whereas primary sensory areas are sparsely innervated (Lewis et al. 1987).

In conclusion, the complex action of levodopa by activation of both D1 and D2 like receptors on synaptic and consequently cortical plasticity makes it difficult to draw general conclusions about its capabilities to enhance learning. Accordingly, as shown in the current study, levodopa can—in a dose-dependent manner—even block improvements in tactile performance induced by peripheral stimulation. Independent of the underlying mechanisms that account for the differential effectiveness of levodopa, the present data make it unlikely that the previously described beneficial effects of amphetamine on coactivation-induced changes in tactile acuity are mediated by the dopaminergic system (Dinse et al. 2003). It therefore remains to be clarified what mechanisms are behind the specific actions of amphetamine in the tactile domain, and what role other neuromodulators such as serotonine and noradrenaline might play in the improvement of tactile perception.

Acknowledgment This work was supported by the International Graduate School of Neuroscience (IGSN), Ruhr-University Bochum and the Sophie und Fritz Heinemann Stiftung. We are grateful to Dr. S. Lissek for editorial assistance.

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